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Investigation of serum prostate-specific antigen levels in pregnant women with gestational diabetes mellitus; a cross-sectional, case-control study

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ABSTRACT

Aims: While many studies are showing that low serum prostate-specific antigen (PSA) levels are associated with the development of diabetes in male subjects, serum PSA levels in women with diabetes have not yet been investigated. Based on this information, we aimed to investigate serum PSA levels in pregnant women diagnosed with gestational diabetes mellitus (GDM).

Methods: This cross-sectional, case-control study was conducted with 88 pregnant women aged between 18 and 39 who applied to Ümraniye Training and Research Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkiye, between May 2023 and September 2023. While the GDM group consisted of 44 pregnant women diagnosed with GDM between the 24th and 28th weeks of pregnancy, the control group consisted of 44 healthy pregnant women with normal 75-g oral glucose tolerance test (OGTT) results. Both groups were compared in terms of serum PSA levels.

Results: GDM and control groups were similar in terms of demographic features (p>0.005). The gestational week and BMI at blood sampling for serum PSA level were similar in the two groups (p=0.801, p=0.383, respectively). The median serum PSA level was found to be 1.22 ng/ml in the GDM group, while it was determined as 1.36 ng/ml in the control group (p=0.155).

Conclusion: The serum PSA level was lower in the GDM group than in the non-GDM group, yet this difference was not significant. Although the number of participants is too small to draw a definitive conclusion, serum PSA does not appear to be involved in the pathophysiology of GDM.

Keywords: Diabetes mellitus, gestational diabetes mellitus, pregnancy, prostate-specific antigen

INTRODUCTION

Synthesized primarily by the prostate gland's epithelial cells, prostate-specific antigen (PSA) acts to liquefy the seminal coagulum by degrading fibronectin and seminogelin, which allows the motile spermatozoa to be released.[1] PSA, which is thought to be specific to the prostate gland, has been used extensively over the years for the diagnosis and follow-up of both benign and malignant prostate diseases.[2] The use of highly sensitive immunoassays has shown that PSA is expressed in tissues beyond the prostate, and importantly, it is now detectable and measurable in females. Apart from the prostate gland, PSA is also expressed in normal lung tissue and lung tumors, primary and metastatic melanomas, pituitary tissue, and adenocarcinoma of the colon. In women, it has been shown that PSA is expressed in the endometrium, normal breast tissue, benign breast diseases, breast cysts, breast fluid, breast cancer, amniotic fluid during pregnancy, and breast milk.[3]

Diamandis et al.[4] were the first to discover that PSA levels in female serum are significantly lower, about 1000 times less, compared to those in male serum. According to reports, the normal range for PSA in women is ≤0.01 µg/L.[3] Following the discovery that PSA is present in breast tissue and detectable in serum, numerous studies have been conducted on its utility in diagnosing and monitoring both benign and malignant breast conditions in women.[5,6] Also, studies have shown that serum PSA levels vary throughout the menstrual cycle.[7,8] Interestingly, the literature has accumulated sufficient studies to allow for a meta-analysis on the effectiveness of PSA in diagnosing polycystic ovary syndrome (PCOS).[9]

Studies conducted over the years have shown that there is an inverse relationship between prostate cancer and diabetes mellitus (DM) in male subjects.[10,11] Although this inverse relationship is not clearly explained, different hypotheses have

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been proposed. While some researchers suggest that chronic diabetes might lower testosterone levels, others argue that the vascular damage diabetes causes in the prostate may have a protective effect by restricting tumor growth.[12,13] The only thing clearly shown among these hypotheses is that lower serum PSA levels are detected in individuals with DM than those without DM.[14] Additionally, research indicates that the duration of diabetes adversely affects the serum PSA level in patients.[15,16] It is unclear why PSA is lower in male individuals with DM than in individuals without DM. It is suggested that high body-mass index (BMI), low testosterone levels in DM, impaired kidney functions due to DM, or medications used such as metformin may be responsible for low serum PSA levels.

Despite this apparent relationship between DM and PSA in male subjects, there is no data in the literature about serum PSA levels in female individuals with DM or pregnant women with gestational diabetes mellitus (GDM). Given this, our goal was to examine serum PSA levels in pregnant women diagnosed with GDM, hypothesizing that these levels would be lower in women with GDM compared to those without GDM.

METHODS

Approval for the study was granted by the Local Ethics Committee at İstanbul Ümraniye Training and Research Hospital (Date: 25.04.2023, Decision No: B.10.1.TKH.4.34.H.GP.0.01/137). The study followed the guidelines set out in the Declaration of Helsinki. All participants provided informed and written consent.

This cross-sectional, case-control study involved 88 pregnant women aged 18 to 39 years who applied to the Department of Obstetrics and Gynecology at Ümraniye Training and Research Hospital in İstanbul, Turkiye, from May 2023 to September 2023. The GDM group included 44 pregnant women diagnosed with GDM between the 24th and 28th weeks, whereas the control group comprised 44 pregnant women with normal results on a 75-g oral glucose tolerance test (OGTT). To control for potential confounding factors, the control group was matched with the GDM group in terms of age, BMI, gestational age, and gender of the fetus.

Participants with any pregestational diseases or a history of GDM in previous pregnancies were excluded from the study. Additionally, individuals who were smokers, had multiple pregnancies, or conceived through in vitro fertilization were also not included in the study. Those who developed any pregnancy-related disease were not included in the study. Those with PCOS or those without PCOS but with clinical findings of hyperandrogenism were not included in the study. Those with existing or previous benign or malignant breast disease or a history of breast surgery were not included in the study.

All participants underwent a 75-g OGTT between 24 and 28 weeks of gestation. The OGTT results were assessed based on the criteria set by the International Association of Diabetes and Pregnancy Study Groups. GDM was diagnosed if one of the following threshold values was met or exceeded: fasting glucose ≥92 mg/dl, 1-hour glucose ≥180 mg/dl, or 2-hour glucose ≥153 mg/dl.[17]

Age, BMI, obstetric history, laboratory and ultrasound findings, and perinatal outcomes for each participant were recorded.

Peripheral venous blood samples were taken from the participants in the morning hours after a minimum of 8 hours of fasting to analyze serum PSA levels within a week after the OGTT was performed. The blood samples collected were processed in accordance with the manufacturer's instructions for the PSA commercial kit used in the study. After standing at room temperature for 20 minutes, the samples were centrifuged at 2000 rpm for 20 minutes. The serum, collected from the upper part of the biochemistry tube post-centrifugation, was transferred to an Eppendorf tube and kept at -80°C. The Human Prostate Specific Antigen ELISA Kit (Sunredbio, Shanghai, China, Catalog No: 201-12-1714) was used to study serum PSA levels using the enzyme-linked immunosorbent assay technique. The kit provided a measurement range from 0.05 ng/ml to 10 ng/ml and had a sensitivity of 0.041 ng/ml. Inter- and intra-assay coefficients of variability of the kit were <12% and <10%, respectively.

Power analysis was performed using the G*power (v3.1.9.2) program to determine the sample size. The power of the study is expressed as 1-β (β=type II error probability). Based on the study conducted by Chen et al.[18], the effect size was calculated as d=1.575 as a result of the calculation made according to the difference in PSA measurements in the diabetes groups. It was calculated that there should be at least 22 participants in each group, 44 participants, to obtain 99% power at the α=0.01 level. Considering the possible dropouts during the study, 44 participants were included in each group. Since there was no dropout at the end of the study, the study was designed with 88 participants (44 in the GDM group and 44 in the control group).

Statistical Analysis

The data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 25.0. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Descriptive statistics were used to summarize the study data, including mean, standard deviation, median, minimum, maximum, frequency, and ratio. An independent t-test was used to compare two groups with parametric distributions, while the Mann-Whitney U test was used for non-parametric distributions. One-way ANOVA was used for comparing more than two groups with parametric distributions, and the Kruskal-Wallis test was used for non-parametric distributions. Correlation analysis was performed to explore relationships between quantitative variables, and the Chi-square test was used for categorical data. A p-value of less than 0.05 was considered statistically significant for all tests.

RESULTS

This study evaluated and compared the serum PSA levels between 44 pregnant women with GDM and 44 without GDM. There were no significant differences between the groups regarding age, pre-pregnancy BMI, total weight gain during pregnancy, BMI at delivery, gravida, and parity ($p>0.05$ for all). The GDM group had significantly higher fasting, 1-hour, and 2-hour glucose levels on the OGTT and higher HbA1c levels than the control group ($p<0.001$ for all). There were no significant differences in gestational age at delivery, delivery mode, newborn gender, or birth weight between the groups ($p>0.05$ for all). The GDM group had a significantly

lower 1st-minute Apgar score compared to the control group; however, the 5th-minute Apgar score, rates of NICU admission, incidence of neonatal hypoglycemia, and cases of neonatal hyperbilirubinemia were similar across both groups (p=0.008, p=0.057, p=0.496, p=0.120, p=0.093, respectively) (**Table 1**).

There were no significant differences in gestational age and BMI at the time of blood sampling for serum PSA levels between the two groups (p=0.801 and p=0.383, respectively). The median serum PSA level was 1.22 ng/ml in the GDM group compared to 1.36 ng/ml in the control group, with a p-value of 0.155 (**Table 2**).

Table 2. Comparison of GDM and control groups in terms of serum PSA levels

	Control group (n=44)	GDM group (n=44)	
	Mean±SD median (min-max)	Mean±SD median (min-max)	p
Gestational week at blood sampling	26.3±1.1 26 (24-28)	26.3±1.4 27 (24-28)	0.801
BMI at blood sampling (kg/m²)	25.1±3.2 24.9 (19.4–29.7)	25.7±2.3 25.3 (22–29.9)	0.383
Serum PSA (ng/ml)	2.28±1.81 1.36 (0.96–6.99)	2.49±2.59 1.22 (0.67–10)	0.155

Mann-Whitney U test, GDM: Gestational diabetes mellitus, PSA: Prostate-specific antigen, BMI: Body-mass index, Min: Minimum, Max: Maximum, SD: Standard deviation

DISCUSSION

The study focused on serum PSA levels in pregnant women with and without GDM. In line with our initial hypothesis, we observed a lower median serum PSA level in the GDM group compared to the non-GDM group, but this difference was not statistically significant.

Waters et al.[19] investigated the association between diabetes and prostate cancer risk in a multi-ethnic cohort. They found that the mean PSA levels were significantly lower in individuals with diabetes than those without diabetes (1.07 ng/ml and 1.28 ng/ml, respectively; p=0.003).[19] In 2009, Müller et al.[20] published a study investigating the relationship between diabetes, BMI, and serum PSA levels. The study involved 778 men aged 50 to 74 randomly selected from a large population-based cohort study conducted in Germany between 2000 and 2002. While the median serum PSA level was 1.0 ng/ml in diabetic men, it was 1.3 ng/ml in non-diabetic men. Also, there was a significant decrease in mean PSA levels in individuals with high (6.1-6.9%) and very high (7%) HbA1c compared to individuals with normal HbA1c values (16% and 30%, respectively).[20]

In 2017, Al-Asadi et al.[16] published a study comparing 70 diabetic and 70 non-diabetic subjects in terms of serum PSA levels. The study found that the mean serum PSA level was significantly lower in diabetic men than in non-diabetic men (1.97 ng/ml and 2.60 ng/ml, respectively, p=0.001). Additionally, age was significantly associated with PSA levels in non-diabetic men. Still, no such relationship was observed in diabetic men.[16] In a paper published by Kobayashi et al.[21] in 2020, among 14486 male individuals who applied to the hospital for routine health screening, median serum PSA levels were found to be significantly lower in 1403 patients with DM compared to 13083 individuals without DM (0.77 ng/ml and 0.81 ng/ml, respectively; p=0.005). After adjusting age,

Table 1. Comparison of GDM and control groups in terms of demographic characteristics, laboratory findings, and perinatal outcomes

		Control group (n=44)	GDM group (n=44)	
		Mean±SD median (min-max) n (%)	Mean±SD median (min-max) n (%)	p
Age (years)		29.14±4.75	30.09±6.09	0.414[m]
Pre-pregnancy BMI (kg/m²)		23.3 (18.2–29.3)	23.7 (20–29.5)	0.488[n]
Weight gained throughout pregnancy (kg)		12.5±5.2	13.5±5.3	0.357[m]
BMI at delivery (kg/m²)		28.4±3.2	29.3±3.3	0.229[m]
Gravida		2.3±1.6	2.3 ±1.5	1.00[m]
Parity	Multiparous	23 (52.3)	29 (65.9)	0.193[p]
	Nulliparous	21 (47.7)	15 (34.1)	
75 g OGTT fasting blood glucose level (mg/dl)		83.5 (70–92)	92 (73–138)	<0.001[n]
75 gr OGTT 1st-hour blood glucose level (mg/dl)		129.2±24.5	180±40	<0.001[m]
75 g OGTT 2nd-hour blood glucose level (mg/dl)		102±18.1	144.8±35.7	<0.001[m]
HbA1c (%)		4.8±0.2	5.2±0.5	<0.001[m]
Gestational age at delivery (weeks)		39±1.7	38.3±2.2	0.340[m]
Mode of delivery	Vaginal birth	20 (45.5)	20 (45.5)	1.00[p]
	Cesarean section	24 (54.5)	20 (45.5)	
Gender of the newborn	Female	16 (36.4)	24 (54.5)	0.087[p]
	Male	28 (63.6)	20 (45.5)	
Birth weight (g)		3191±462.9	3353±521.4	0.128[m]
1st minute Apgar score		8 (5-9)	7 (5-9)	0.008[n]
5th minute Apgar score		9 (7-10)	9 (4-10)	0.057[n]
NICU admission		13 (29.5)	16 (36.4)	0.496[p]
Neonatal hypoglycemia		4 (6.8)	9 (20.5)	0.120[p]
Neonatal hyperbilirubinemia		2 (4.5)	8 (18.2)	0.093[p]

[m] Independent-T test; [n] Mann-Whitney U test; [p] Chi-square test, GDM: Gestational diabetes mellitus, BMI: Body-mass index, OGTT: Oral glucose tolerance test, HbA1c: Hemoglobin A1c, NICU: Neonatal intensive care unit, Min: Minimum, Max: Maximum, SD: Standard deviation

significant decreases in PSA were found, especially in diabetic men taking antidiabetic drugs. Also, it was observed that PSA levels were significantly reduced in diabetic men with higher HbA1c and fasting blood glucose levels.[21]

Unlike the previous studies, other research has indicated that serum PSA levels may be lower in individuals with diabetes than those without, though this difference lacks statistical significance. One such study, conducted by Naito et al.[22], involved 195 diabetic men and 1.977 non-diabetic men. The study reported that the mean serum PSA level was lower in the diabetic group than in the non-diabetic group. However, this difference was insignificant (p=0.286). After adjusting for age and age+BMI, the mean PSA level in the diabetic group was still lower than that in the nondiabetic group, although not statistically significant.[22] Ainahi et al.[23] conducted a study published in 2018 examining 470 diabetic men and 869 non-diabetic men between January 2015 and April 2016. The results showed no significant difference in mean PSA levels between the two groups (1.31±0.04 ng/ml for diabetics vs. 1.36±0.03 ng/ml for non-diabetics; p=0.380). The study also indicated mean serum PSA levels increased with age in diabetic and non-diabetic men.[23]

A meta-analysis published in 2021 reviewed the relationship between serum PSA levels and diabetes, incorporating data from 8 studies. The analysis reported that diabetic patients generally had significantly lower PSA levels compared to non-diabetic individuals. The authors concluded that the observed lower PSA levels in diabetics are more likely related to the duration and severity of the disease or the use of anti-diabetic medications rather than the diabetes diagnosis itself.[14]

Similar to the studies referenced earlier, our findings indicated that the median serum PSA level was lower in the GDM group than in the non-GDM group, but this difference did not achieve statistical significance. Furthermore, we could not establish a significant relationship between serum PSA levels and GDM-related factors, including HbA1c and BMI.

All existing studies on the relationship between serum PSA and diabetes have focused on male subjects, consistently finding lower PSA levels in individuals with diabetes compared to those without. Factors such as age, BMI, duration and severity of diabetes, and treatments used have been shown to influence serum PSA levels in diabetic men. However, no research has yet investigated serum PSA levels in diabetic women. This study is pioneering in assessing serum PSA levels in pregnant women with GDM, and we anticipate it will provide a basis for future studies exploring PSA's role in GDM's pathophysiology.

Limitations

This study has notable limitations, including the small sample size and that serum PSA levels were measured only once. Additionally, the lack of data on how serum PSA levels change throughout normal pregnancy and the absence of follow-up on PSA levels after blood glucose regulation in women with GDM are significant constraints.

CONCLUSION

Our results indicated that the median serum PSA level was lower in the GDM group than in the non-GDM group; however, this difference was not statistically significant. We could not determine a significant PSA cutoff value for GDM diagnosis, but our study suggests that GDM negatively influences serum PSA levels in a currently unexplained way.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for the study was granted by the Local Ethics Committee at İstanbul Ümraniye Training and Research Hospital (Date: 25.04.2023, Decision No: B.10.1.TKH.4.34.H.GP.0.01/137).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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